Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,12,14,15 and 17-27* is/are pending in the application.

4a) Of the above claim(s) *6-10,14,15 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,12,17 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20100113* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 10/23/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments with respect to the rejection under 35 USC 103 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-2, 5, 12, 17 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; cited in a prior Office Action); Gilliland et al. (Gilliland 1) ("The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies"; 1992; Journal of Applied Bacteriology; 72: 252-257; cited in a prior Office Action); Gilliland et al. (Gilliland 2) ("Kinetic evaluation of claimed synergistic paraben combinations using a factorial design"; 1992; Journal of Applied Bacteriology; 72: 258-261; cited in a prior Office Action); and Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578; cited in a prior Office Action); in view of Routledge et al. ("Some Alkyl Hydroxy

Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19; cited in a prior Office Action).

The teachings of DeLongueville, Gilliland 1, Gilliland 2, Doron and Routledge have been outlined on the record, which are repeated here.

DeLongueville teaches the use of an individual optical isomer of cetirizine for preparing a medicament (abstract); such optical isomers include levocetirizine, which contains preferably at least 95% by weight of the levocetirizine (p. 1, lines 29, 32-33); pharmaceutical compositions as liquid compositions in the form of a sterile solution miscible with water (p. 5, lines 12-13); carriers and diluents include water (p. 5, lines 21-22); preserving substances are taught (p. 5, line 15); topical application in the form of an aqueous solution (p. 5, line 30-31); solutions for oral administration (p. 6, lines 1-2); drops in the form of a liquid, with added preservatives (p. 6, lines 5, 7, 9); a syrup for oral formulation is preferred that contains methyl- and propylparaben (methyl parahydroxybenzoate and propyl parahydroxybenzoate) and purified water (p. 6, lines 18-20). DeLongueville does not teach a specific embodiment containing levocetirizine and the required mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate (although each of these components is separately taught); or a total amount of methylparaben and propylparaben or the claimed ratio present in the liquid composition.

Doron teaches the antibacterial effects of methyl and propyl paraben against Streptococcus sobrium, which is involved in tooth dacay in the oral cavity, and that antibacterial synergistic effect was found between several combinations of parabens

(abstract); at 0.03% (about 0.3 mg/mL) propyl paraben (PP), with increasing amounts of methyl paraben, decreasing amounts of viable bacterial counts were demonstrated (p. 577, Figures 1-2), the ratios vary from 0.015:0.03 (1:2) MP:PP to 0.25:0.3 (8.33:1), or almost 9/1. At the highest ratio in both figures no bacterial counts were recorded (Figures 1-2; pp. 576-575, bridging paragraph). Additionally, MP had the largest antibacterial effect of the parabens tested (abstract).

Gilliland 1 teaches the effect of temperature on the kill rate of *Escherichia coli* by methyl and propyl parabens was studied (abstract); in the presence of a bactericidal antimicrobial agent the rate of kill of microbes generally increases as the temperature increases (p. 252, 1st paragraph); a comparison of *E. coli* growth is presented in a chemically defined growth medium, which shows positive growth vs. growth in water as the medium, which shows nearly constant levels of *E. coli*, i.e., little or no growth (p. 254, Figure 2); the effect of temperature on the kill rates and rate constants for inocula prepared from exponential and stationary phase E. coli in the presence of 0.12% w/v methyl paraben and 0.012% w/v propyl paraben in the chemical growth medium (a 10/1 ratio, with total [MP]+[PP]=1.32%; p. 254, Table 1; p. 255, Figures 3, 5); the kill rates are reported for both exponential phase and stationary phase cells (p. 254, Table 1, pp. 255, Figures 3-6); reported activation energies for the effect of a series of antimicrobial agents, including phenol, benzyl alcohol and benzalkonium chloride have been reported from 5 different micro-organisms (p. 256, Table 2).

Gilliland 2 teaches antimicrobial effects of methyl and propyl parabens are investigated to determine whether the parabens act synergistically, that combinations of

methyl or propyl parabens, at concentrations which slow down or inhibit bacterial growth when used singly produced definite kill, the parabens are therefore synergistic since in combination they produce an effect which is not observed when they are used singly, the effect is not considered true synergism as shown by kinetic results of experiments with a factorial design, which indicated no significant interaction between the two parabens (abstract); combinations of antimicrobial agents are widely used both for treating diseases and for preserving pharmaceutical systems, the rationale is that by using combinations the activity spectrum may be broadened and the agents involved may act synergistically, although it is difficult to provide clinical evidence for synergy with in vitro systems (p. 258, 1st paragraph); studies utilized a chemically defined medium, to which methyl and propyl esters of p-hydroxybenzoic acid were added (p. 258, 2nd and last paragraphs); control studies employed 0.012 and 0.014 % w/v propyl paraben, for which growth was observed (p. 259, Table 1; p. 261, Figure 4); at 0.12 and 0.14% w/v methyl paraben the number of E.coli cells remained approximately constant, a bacteriostatic effect (p. 260, Figure 3, 2nd paragraph); combinations of 0.12 or 0.14% w/v methyl paraben with 0.012 or 0.014% w/v propyl paraben all resulted in observable kill of *E. coli*, a bactericidal effect of the paraben combination (p. 259, Table 1; p. 260, 2nd & 3rd paragraphs; p. 261, Figure 5). It is noted that the 4 combinations have a MP/PP ratio of 8.6/1 for 0.12% MP + 0.014% PP; a ratio of 10/1 for 0.12% MP + 0.012% PP or 0.14% MP + 0.014% PP; and a ratio of 11.7/1 for 0.14% MP + 0.012% PP. These ratios bracket the claimed ratio of 9/1, rendering the ratio as an obvious variant of the taught ratios.

Routledge teaches that a range of parabens, including methyl- and butylparaben, are weakly estrogenic, the suggestion is made that the safety in use of these chemicals should be reassessed, with particular attention being made to the estimation of the actual levels of systemic exposure of humans exposed to these chemicals, in order to assess the risk of exposure to parabens (abstract); certain synthetic compounds used in a wide range of products can mimic the main natural estrogen, influencing the expression of estrogen-dependent genes, taken with epidemiological data suggests a progressive decline in human male reproductive health and fertility (p. 12, 1st paragraph); a group of parabens, used extensively in a wide range of products have been studied (p. 12, 2nd paragraph); binding to estrogen receptors is demonstrated for butyl paraben (p. 13, Figure 2); the response of the yeast estrogen screen to propyl and methyl paraben demonstrates that a shifting of about 100-fold higher concentrations of methyl paraben is required as compared to propylparaben in the assay (p. 15, Figure 3); butyl paraben was shown to increase the weight of the uterus in immature rats (p. 15, 3rd paragraph); a discussion of the toxicology of parabens has led to p-hydroxybenzoates being widely permitted in foods in the UK and US at levels of up to 0.1% w/w for MP and PP in food (corresponding to about 1 mg/mL; p. 16, right, 3rd paragraph); maximum levels of parabens in pharmaceutical products seldom exceed 1% w/w, EEC and Danish cosmetic regulations permit the preservation of cosmetic products with MP and PP up to a maximum combined concentration of 0.8% w/w (8mg/mL; p. 16, right, 3rd paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the levocetirizine formulations, including oral liquid formulations and eye drops, as taught by DeLongueville with a synergistic ratio of methylparaben and propylparaben; it would have been obvious to utilize the range of ratios taught by Gilliland 2 including the claimed ratio of 9/1 or to extend the ratios from 8.33:1 taught by Doron to the claimed ratio of 9/1, which is within the Gilliland 2 scope taught or extrapolated from the Doron data; it would also have been obvious to reduce the total amount of MP+PP from the total amounts taught by Gilliland 1 and 2 to a value less than 1%, meeting the claimed total mixture of paraben amounts, while still giving bacteriocidal preservative effect; accomplished by: 1) reducing defined components in the medium that contribute to microbial growth, such as the growth medium identified by Gilliland 1; and/or 2) including a third preservative agent, such as one of the additional agents taught by Gilliland 1 in Table 2, in combination with the 9/1 ratio of MP/PP; both of these approaches would have resulted in the liquid pharmaceutical compositions within the scope of the instant claims, with the antimicrobial properties demonstrated by applicant. The motivation to utilize MP/PP ratio of 9/1 would have been the clear indication of Gilliland that ratios encompassing this are synergistic in terms of bacterial killing and the indication that better killing is observed at higher amounts of MP, relative to PP, illustrated by the killing of the bacterium at the right side of Figures 1 and 2; additionally, utilization of a higher MP/PP ratio, such a 9/1 would employ a significantly smaller amount of PP that binds to estrogen receptors with higher affinity; the motivation to reduce the total [MP]+[PP] to a value less than 1 mg/ml would have been the

recognition of Routledge that parabens mimic natural estrogen, and the levels approved in foods of up to 1 mg/mL would be a target concentration to stay below, while still retaining microbicidal activity; the motivation to combine a 9/1 ratio of MP/PP with an additional antimicrobial agent would have been the expectation of additive or even synergistic microbe killing, as well as the potential for a broader spectrum of microbes that are killed by the combination of preservatives.

As pointed out in MPEP 2144.06 (I), "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…. [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

It is noted that the arguments provided on the record were considered to be persuasive. However, the combination that includes Doron reference is considered to render the instant claims obvious over the references in combination.

Applicant argued that Doron taught the lowest total concentration of the combination of MP and PP to be completely antibacterial is 1.55 mg/ml for liquid, planctonic bacterial growth; that the Examiner agreed that it would have been nonobvious to reduce the concentrations of parabens to less than 1.55 mg/ml, let alone by more than 35%, down to 1 mg/mL; that one of ordinary skill in the art would have avoided using smaller concentrations because they would believe or reasonably expect that such concentrations as presently claimed would render a composition susceptible to bacterial growth. While this line of reasoning is persuasive for the combination of

references, when Doron is not included (based on the combination of DeLongueville, Gilliland 1, Gilliland 2, nd Routledge); however, when the data of Doron is also considered, lower amounts even than 1 mg/mL are considered to be obvious. A review of the data of Figure 1 of Doron indicates that reduced growth of the bacteria tested (e.g. immobilized S. sobrinus) is significantly reduced even at the 0.015 w/v MP amount data point, (corresponding to MP+PP of 0.45 mg/mL). This indicates that some reduction in viable bacteria would be expected even at low total amounts, or providing a motivation to include MP and PP even at lower amounts. There is a specific reason to keep the paraben amounts low, below 1 mg/mL, which is based on the recognition of estrogenic activity and the argument for reassessment of safety levels taught by Routledge, that is suggestive of levels lower than the GRAS levels, even though regulations permit higher levels. This motivates a combined amount present of less than 1 mg/mL. It would have been clear to one of ordinary skill in the art that there is still an antimicrobial benefit to use of lower amounts. The data point of Figure 1, at 0.06 w/v% MP (corresponding to 0.9 mg/mL MP + PP, within the claimed range) demonstrates around 1% bacterial growth; this amount of bacterial growth would still provide a benefit to a formulation, rendering a 9/1 ratio where the total of MP+PP as obvious; additionally, the addition of a third active agent would result in further killing at the lower paraben concentrations.

With regard to the argument of an unexpected result of total killing, several points may be made. 1) The comparison of the data in the specification to the Doron data is not a direct comparison; Doron and the data presented in the instant specification test

the growth of different organisms; applying a cutoff point from Doron as unexpected to a completely different set of organisms is an improper comparison to demonstrate a result is unexpected; 2) The combination of MP+PP at a 9/1 ratio where the total amount of the two parabens is less than 1.125, less than 1 mg/ml, or even 0.75 mg/mL would still be expected to be completely antimicrobial when another preservative agent is present with MP and PP, such as one of the Gilliland 1, Table 2 active agents. When a combination of MP+PP and a third antimicrobial agent are used, lower total [MP]+[PP] will be expected to result in an antimicrobial effect. 3) The data argued to be unexpected, disclosed in the specification, are not commensurate in scope with any of the claims under examination, which utilize open language (comprising, permitting even other antimicrobial agents) and are not limited to the amounts of the claimed components in any of the claims under examination; the solutions tested all contain additional ingredients at specific amounts (as disclosed in Table 4) that are not recited in any of the claims.

Applicant's argument that the GRAS level is unrelated to the effectiveness may be the case; however, the argument that lower levels are better, made by Routledge, because of the estrogenic activity of the parabens provides a significant motivation to keep the total amount of parabens lower than the GRAS level; optimization of the conditions and the addition of a third preservative/antimicrobial agent would permit an antimicrobial composition with less than 1% bacterial growth; i.e., one of ordinary skill in the art would not have ignored the Routledge teaching which clearly teaches a potential problem with higher levels of parabens. Such a composition is within the scope of the

instant claims, and <1% growth is not considered unexpected for three antimicrobial agents that include MP and PP at the required amounts.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/

Examiner, Art Unit 1628